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Pediatric Cardiology

Clinical Features of Isolated Noncompaction of the Ventricular Myocardium

Long-term Clinical Course, Hemodynamic Properties, and Genetic Background

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OBJECTIVES A nationwide survey was conducted to clarify the clinical features of isolated noncompaction of the ventricular myocardium (INVM) in Japanese children in comparison with features previously described in patients with INVM.

BACKGROUND Isolated noncompaction of the ventricular myocardium is a rare disorder characterized by an excessively prominent trabecular meshwork. It is accompanied by depressed ventricular function, systemic embolism and ventricular arrhythmia.

METHODS A questionnaire specifically designed for this study was sent to 150 hospitals in Japan where a pediatric cardiology division exists.

RESULTS Twenty-seven patients were diagnosed by two-dimensional echocardiography, their ages ranging from one week to 15 years at presentation, with follow-up lasting as long as 17 years. The gross anatomical appearance and the extension of noncompacted myocardium predominantly at the apex observed on two-dimensional echocardiograms were similar to observations reported previously. Dissimilarities included a greater number of asymptomatic patients at initial presentation, a longer clinical course with gradually depressed left ventricular function, no systemic embolism, and rare ventricular tachycardia in the Japanese children. Cardiac catheterization disclosed normal left ventricular end-diastolic volume and increased left ventricular end-diastolic pressure in most cases, consistent with restrictive hemodynamics. A higher incidence of Wolff-Parkinson-White syndrome was found in the children, whereas left bundle branch block was rarer than reported in adults. Familial recurrence was high (44%) and included many women.

CONCLUSIONS In Japanese children, INVM can be found by screening examinations at asymptomatic stage, and it might have a longer clinical course with gradually depressed left ventricular function and restrictive hemodynamics. The pattern of familial recurrence we observed implies that INVM is a distinctive clinical entity with a heterogeneous genetic background. (J Am Coll Cardiol 1999;34:233–40) © 1999 by the American College of Cardiology

The noncompacted ventricular myocardium, characterized by excessively prominent trabecular meshwork and deep intertrabecular recesses, is seen in the early period of embryogenesis (1,2). Although similar myocardial patterns of "persisting sinusoids" are frequently reported in association with congenital heart anomalies such as pulmonary atresia with intact ventricular septum (3–7), isolated noncompaction of the ventricular myocardium (INVM) is rare. It occurs in the absence of other structural heart diseases and is thought to be due to an arrest of myocardial morphogenesis (8–17). The recesses in INVM are lined with endothelium continuous with the ventricular endocardial endothelium and are histologically different from persisting intramyocardial sinusoids, which are in continuity with the

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Abbreviations and Acronyms

A-V block	= atrioventricular block
DCM	= dilated cardiomyopathy
ECG	= electrocardiogram
INVM	= isolated noncompaction of the ventricular myocardium
LBBB	= left bundle branch block
PSVT	= paroxysmal supraventricular tachycardia
PVC	= premature ventricular contraction
RBBB	= right bundle branch block
RCM	= restrictive cardiomyopathy
WPW	= Wolff-Parkinson-White

coronary circulation (11). In the relatively small number of pediatric cases of reported INVM, the clinical manifestations were left ventricular failure, systemic arterial embolism and severe arrhythmias (11). The long-term prognosis, hemodynamic properties and genetic nature of INVM, however, remain largely unknown.

Recent studies on genetic linkage analysis has revealed that mutations in the gene G4.5 on the Xq28 chromosomal region are responsible for INVM and that this disorder is allelic with Barth syndrome (X-linked disorder associated with dilated cardiomyopathy, skeletal myopathy, neutropenia and abnormal mitochondria) (18–21). It is important to note that women with INVM were observed in our series, suggesting the possible non-X-linked inheritance in some instances.

From the inception of a heart disease screening program for school children in Japan, various arrhythmias and cardiomyopathies have been detected in asymptomatic stages (22–24). It is not surprising that INVM might be detected in such mass screenings. We identified and analyzed a large series of patients with INVM via a nationwide survey, including many asymptomatic patients identified by mass screening and the familial clusters with affected females. In this report we describe the clinical characteristics and the genetic background of INVM in Japanese children and compare our results with those of previous reports (11,17).

METHODS

We conducted a nationwide survey to elucidate the clinical features of INVM in Japanese children. A questionnaire designed specifically for this study was sent in October 1996 to 150 hospitals in Japan that house a division of pediatric cardiology. The questionnaire included questions concerning clinical presentation and symptoms; primary diagnosis; a personal and family history. Other associated findings included developmental delay and facial dysmorphism; findings of scalar electrocardiogram (ECG); two-dimensional Doppler, and color Doppler echocardiography; cardiac catheterization; other imaging modalities such as thallium-201 myocardial imaging, magnetic resonance imaging and ultra-fast computed tomography; myocardial biopsy; and details of clinical course. The surveys were returned to us between October 1996 and February 1997 and included data on 29 patients from 16 hospitals. Information on the completed questionnaires was confirmed or expanded by telephone or facsimile communication with the hospital personal reporting patients with INVM.

A diagnosis of INVM was made according to 1) the characteristic appearance of numerous, excessively prominent trabeculations and deep intertrabecular recesses on echocardiography, as previously described (11,17); and 2) the disease process observed in one or more ventricular wall segments. Cardiac anomalies that sometimes exhibit the similar myocardial pattern of persistent sinusoids, such as ventricular outflow tract obstruction, were excluded. Echocardiography videotapes were reviewed and interpreted by one author (F.I.) to confirm the diagnosis. Echocardiographic data included left ventricular end-diastolic dimensions; fractional shortening or ejection fraction; and left ventricular free-wall thickness and interventricular septal thickness, in accordance with the recommendations of the American Society of Echocardiography (25). The distribution of prominent trabeculations in the left ventricle was assessed using parasternal, apical, and subxiphoid imaging planes. To quantify the extension of trabecular meshwork, the thickness of the left ventricular wall and X-to-Y ratios were measured at the levels of mitral valve, papillary muscles, and apex, according to the methods reported by Chin et al. (11), where X represents depth of the trabecular recess and Y represents total free-wall thickness to the peak of the trabeculation.

Cardiac catheterization data included left ventricular end-diastolic pressure and pulmonary arterial pressure. Left ventricular end-diastolic volume and ejection fraction were derived from left ventriculography using Simpson's method, indexed for body size. The morphologic appearance of both ventricles was also assessed by angiography.

Baseline scalar ECG was interpreted based on normal ECG standards for infants and children (26). In addition, Wolff-Parkinson-White (WPW) syndrome was diagnosed based on documented spontaneous ventricular pre-excitation; individuals with a PR interval <100 ms plus abnormal QRS vector or bundle branch block were diagnosed having possible pre-excitation (27). Thallium myocardial imaging, endomyocardial biopsy, magnetic resonance imaging, and ultra-fast computed tomography findings were also assessed when applicable.

Wall thicknesses of the left ventricle and X-to-Y ratios were summarized as mean ± SEM. Statistical analysis was performed using one-way analysis of variance to compare wall thickness and X-to-Y ratios at the levels of mitral valve, papillary muscles and apex. The X-to-Y ratios at matched levels were compared with those reported by Chin et al. (11) using the Student unpaired *t* test. The occurrence of events, including systemic embolism, ventricular tachycardia, WPW syndrome and left bundle branch block (LBBB) on scalar ECG was com-

Table 1. Patient Characteristics

Case	Age at Presentation (yrs)	Gender	Clinical Presentation	Familial Recurrence	Associated Findings	Follow-up Periods (yrs)	Outcome
1	Neonate	F	ECG	Sister, father, gfather	FD, DD	4	DSF
2	Neonate	F	ECG	Sister, father, gfather	FD, DD	4	DSF
3	Neonate	M	Pre-op exam	Brother	FD, DD	13	DS & DF
4	12	M	·School ECG	Brother	FD, DD	5	DS & DF
5	2	F	Dyspnea, syncope	Brother, cousin	—	17	DS & DF, PVC
6	6	F	·School ECG	Sister, cousin	—	12	DSF, PVC
7	10	M	Family history	Sister, cousin	—	7	DSF, PVC
8	13	F	Family history	Sister, cousin	—	3	DSF
9	3	F	Arrhythmia	Sister	—	4	III AV block
10	9	F	Palpitation	Sister	—	1	PVC
11	12	M	·School ECG	Brother	—	3	PVC
12	12	M	Family history	Brother	—	1	—
13	0.2	F	HM, WPW, PSVT	—	FD	11	DSF, PH
14	0.2	F	cWPW, PSVT	—	—	6	—
15	0.4	M	Af	—	FD, DD	2	—
16	0.8	F	HM	—	Scoliosis	7	DSF
17	2.8	M	Pre-op ECG	Brother (RCM)	FD	0.2	DSF, PVC
18	2.9	M	Tachypnea, WPW	—	Cataract	8	DSF
19	3	F	HM	—	—	8	—
20	4	M	HM, WPW	—	—	4	—
21	5	M	HM	—	Cleft palate	10	PVC
22	5	M	HM	—	—	13	Died
23	6	M	·School ECG	—	—	17	—
24	7	M	·School ECG	—	—	12	DSF
25	12	F	·School ECG	Father (HCM)	—	10	DS & DF
26	12	M	Dyspnea	—	—	1	Died
27	15	M	·School HM	—	—	0.3	—

Pre-op exam = pre-operative examination; HM = heart murmur; cWPW = concealed WPW syndrome; Af = atrial fibrillation; gfather = grandfather; RCM = restrictive cardiomyopathy; HCM = hypertrophic cardiomyopathy; FD = facial dysmorphism; DD = developmental delay; DSF = decreased systolic ventricular function; DS & DF = decreased systolic and diastolic ventricular function; PH = pulmonary hypertension; PVC = premature ventricular contraction; PVST = paraxysmal supra-ventricular tachycardia.

pared with the current study group and either those previously reported by Chin et al. (11) or Ritter et al. (17) using the Fisher exact test. Differences were considered significant when the p value was less than 0.05.

RESULTS

Patient characteristics. Out of 29 patients originally reported, 27 were confirmed with INVM (15 male and 12 female) and were included in this study. The other two patients had only mild trabeculations within one ventricular wall segment and were excluded from the current study. Ages at presentation ranged from one week to 15 years (median, five years), with follow-up being as long as 17 years (median, six years) (Table 1).

Although six patients had clinically overt signs or symptoms of heart failure such as dyspnea at initial presentation, the other patients were asymptomatic but were identified because of abnormalities on screening ECG (Table 1). Among these asymptomatic patients, seven patients were identified through school screening examinations and three of these seven patients were probands in three families (cases 4, 6, and 11; Table 1).

The primary diagnosis of INVM was missed in most cases. The diagnosis of INVM was delayed because of the mistaken similarities between INVM and other cardiomyopathies and the examiner's unfamiliarity with its specific diagnostic pattern. Incorrect diagnoses included dilated cardiomyopathy (DCM) (n = 10), hypertrophic cardiomyopathy (n = 4), dilated-phase hypertrophic cardiomyopathy (n = 3), apical hypertrophic cardiomyopathy (n = 1), endocardial fibroelastosis (n = 3), restrictive cardiomyopathy (RCM) (n = 1), myocarditis (n = 1) and arrhythmia (n = 1). The most recent three patients were diagnosed primarily with INVM. Several echocardiographic examinations were required to diagnose INVM in most of the cases.

Electrocardiography. Twenty-two patients (88%) showed abnormalities on baseline ECG including ST depression and flat or negative T waves in leads II, III, aV_F, and V_{4-6}, and right bundle branch block (RBBB) (Table 2). The QRS

Table 2. Electrocardiographic and Echocardiographic Data

Case	Electrocardiographic Findings	Arrhythmia	Site of Noncompaction	LV Dilation	LVEF (%)
1	Neg. T in II, III, aVf, V5-6		LV all	—	63
2	Neg. T in II, III, aVf, V5-6		LV all	—	60
3	LAD, flat T, in II, III, aVf		LV apex, IW, PW	—	77
4	LAD, QS in V1-2, flat T in II, III, aVf		LV apex, IW, PW	+	63
5	CVH, flat T	PVC	LV apex	—	56
6	LAD	PVC	LV all	+	64
7	LAH	PVC	LV apex	+	52
8	nl		LV apex	—	nl
9	LVH	II AV block	LV apex, IW, PW	—	75
10	ST dep. in V6	PVC	LV apex, IW, PW	—	80
11	LAD, neg. T in V5-6	PVC	LV apex, IW	+	67
12	nl		LV apex, IW	—	75
13	WPW	PSVT	LV apex, IW, PW	—	66
14	Concealed WPW, neg. T in III, aVf	PSVT	LV apex, IW, PW	+	41
15	LAD, RAH, RVH	Af	LV all, RV	+	49
16	RBBB, neg. T in aVf, V5-6	II AV block	LV all	—	dec
17	LBBB	PVC	LV apex	+	44
18	WPW		LV all	+	55
19	ST elevation		LV all	—	74
20	WPW		LV all	—	dec
21	PVC	PVC	LV apex, IW	—	nl
22	LAD, LAH, RBBB	III AV block	LV apex	—	75
23	ST dep, neg. T in II, III, aVf, V5-6		LV apex, PW, LW	—	72
24	RBBB		LV, RV apex	—	66
25	ST dep, neg. Tin II, III, aVf, V4-6		LV apex, PW	+	nl
26	CVH, CAH, neg. T in II, III, aVf		LV, RV apex	—	40
27	Sinus bradycardia		LV apex, PW, RV	—	63

neg. T = negative T wave; LAD = left axis deviation; CVH = combined ventricular hypertrophy; LAH = left atrial hypertrophy; nl = normal; LVH = left ventricular hypertrophy; ST dep = ST depression; RAH = right atrial hypertrophy; RVH = right ventricular hypertrophy; LBBB = left bundle branch block; RBBB = right bundle branch block; CAH = combined atrial hypertrophy; LV = left ventricle; IW = inferior wall; PW = posterior wall; LW = lateral wall; RV = right ventricle; EF = ejection fraction.

duration ranged from 50 to 140 ms (mean 80 ms). The incidence of WPW syndrome was high (15%), being manifested in three patients and concealed in one patient; in contrast, the incidence of LBBB was rarer than those reported among adults ($p < 0.05$) (17). Although various arrhythmias were recognized during the clinical course in 13 patients, including paroxysmal supraventricular tachycardia (PSVT) with WPW syndrome (Table 2), ventricular tachycardia was rarer than that reported previously in children (11) and adults (17) ($p < 0.05$ and $p < 0.01$, respectively).

Echocardiographic findings. Trabecular meshwork was observed predominantly at the inferoapical region on two-dimensional echocardiography (Table 2). The maximum wall thickness was observed in the same region (20.8 ± 0.7 mm); the thickness of the interventricular septum and the wall thickness at the mitral valve and papillary muscle levels were 6.1 ± 0.3 mm, 7.6 ± 0.3 mm, and 15.4 ± 0.7 mm, respectively ($p < 0.0001$). Similarly, the maximum extension of the trabecular meshwork, that is, the minimum X-to-Y ratio, was observed in the apex (0.27 ± 0.01); the X-to-Y ratios at the mitral valve and papillary muscle levels were 0.84 ± 0.04 and 0.43 ± 0.02, respectively ($p < 0.0001$). The minimum X-to-Y ratio in the current study was comparable to that of the previous study by Chin et al. (11) (0.20 ± 0.11).

The disease process was observed in both the right and left ventricles in four patients. Left ventricular endocardial thrombi were not detected in any of the patients. Color Doppler study disclosed typical forward and reversed flow between prominent trabeculations during the cardiac cycle (Fig. 1). Systolic function of the noncompacted ventricular myocardium was depressed in most cases, whereas the function was well preserved at the papillary muscle level of the left ventricle (Table 2). The ejection fraction of the left ventricle obtained by the Pombo method ranged from 40% to 77% (mean 61.5%) (Table 2). Depressed left ventricular systolic function at the papillary muscle level was observed with echocardiography in 13 patients (48%) at first presentation. Another six patients (25%) had gradually depressed left ventricular systolic function during the follow-up period. Twelve out of 15 patients (80%) with a follow-up period longer than five years and eight out of nine patients (89%) with a follow-up period longer than 10 years developed depressed left ventricular systolic function. Decreased E/A wave ratios in mitral inflow consistent with impaired

diastolic function of the left ventricle (28) were suggested in recent two-dimensional and Doppler echocardiographic studies in six patients.

Cardiac catheterization. Cardiac catheterization disclosed depressed left ventricular systolic function in 16 patients (Table 3). Increased left ventricular end-diastolic pressure was observed in 15 patients (range 12 to 34 mm Hg) and pulmonary hypertension in five patients (mean pulmonary arterial pressure [PAP] 28 to 70 mm Hg). However, left ventricular end-diastolic volume was normal in 14 patients (range 72% to 129% of normal; mean 97%), and exceeded 130% of normal in only four patients, which implies impaired distensibility of the left ventricle.

Left ventriculography demonstrated the sponge-like appearance of the noncompacted ventricular wall during the diastolic phase and marked retention of the contrast medium in the intertrabecular recesses during the systolic phase. In addition, hypokinesis of the noncompacted ventricular wall was notable in most cases. In one patient, diverticular configuration of the noncompacted ventricular wall was observed.

Table 3. Cardiac Catheterization Data

Case	LVEDV (% of normal)	EF (%)	LVEDP (mm Hg)	Mean PAP (mm Hg)
3	109	44	9	23
4	129	55	14	16
5	91	54	30	43
6	120	33	17	15
7	89	54	22	17
9	122	68	16	17
10	73	61	15	20
11	132	58	8	12
13	85	24	16	35
14	162	47	22	ND
16	230	62	12	17
17	152	47	12	20
19	125	60	7	18
21	99	60	18	23
22	75	46	23	27
23	80	56	20	28
24	96	65	12	15
26	72	45	34	75

LVEDV = left ventricular end-diastolic volume; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; PAP = pulmonary arterial pressure; ND = not done.

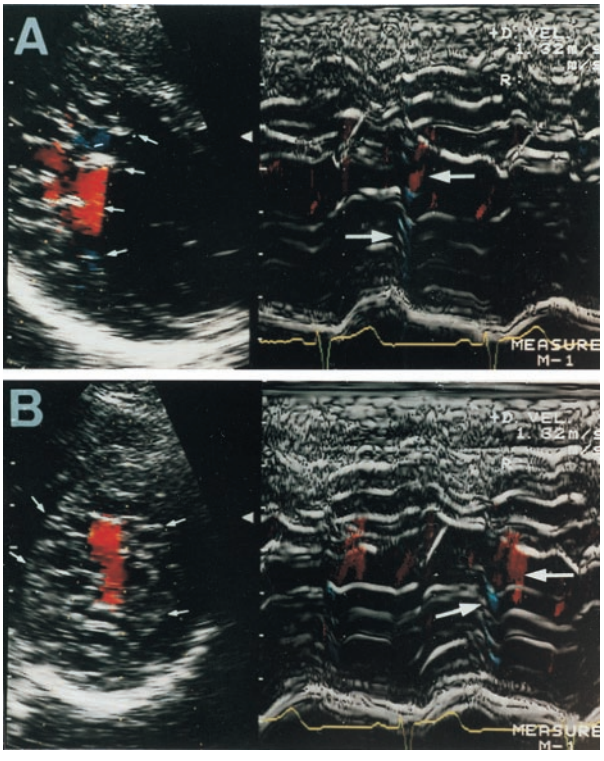

Figure 1. A representative echocardiogram in a patient with INVM (case 3, Table 1). Two-dimensional echocardiogram demonstrates numerous prominent trabeculations (small white arrows) and intertrabecular recesses in the apex and free wall of the left ventricle in the parasternal long-axis view **(A)** and in the parasternal short-axis view **(B).** Color Doppler and M-mode echocardiogram show typical forward (red color, white arrow) and reversed flow (blue color, white arrow) between prominent trabeculations during the cardiac cycle.

Thallium myocardial imaging. Thallium-201 myocardial imaging was performed in 14 patients at rest and disclosed a hypoperfusion area in the left ventricle corresponding to the zones where noncompacted ventricular myocardium can be localized in all patients. Findings were normal in five patients.

Magnetic resonance imaging. Magnetic resonance imaging was performed in 11 cases and disclosed inner zones of noncompacted myocardium distinguishable in most cases from thin outer zones of compacted myocardium. The T2-weighted imaging in two cases revealed high-intensity areas at the apex of the left ventricle, consistent with disturbed microcirculation due to fibrosis, thrombus formation and hypokinesis of this area (Fig. 2).

Ultra-fast computed tomography. Ultra-fast computed tomography was performed in five cases, showing early defects and rate enhancement of the noncompacted ventricular myocardium, implying fibrosis in this area.

Endomyocardial biopsy. Endomyocardial biopsy was performed in 12 cases, from the right ventricle in 8 cases, from the left ventricle in 2, and from both ventricles in 2. A wide range of interstitial fibrosis was observed in eight cases, endomyocardial thickening and subendocardial fibroelastosis in four cases, myocyte hypertrophy in two cases, and intramural thrombosis in one case.

Familial recurrence. Familial recurrence was higher in our study group than that previously reported in adults ($p < 0.005$) (17) and was present in 12 patients (44%), including six sets of siblings (cases 1 and 2; 3 and 4; 5 and 6; 7 and 8;

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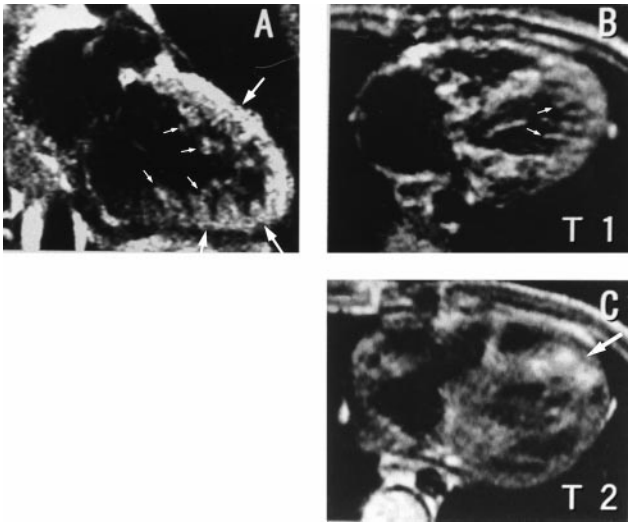

Figure 2. A representative magnetic resonance image (MRI) of a patient with INVM (case 3, Table 1), T1-weighted coronal image **(A)** and axial image **(B)** of the left ventricle. An inner zone of noncompacted myocardium (small white arrows) is distinguishable from a thin outer zone (white arrows) of compacted myocardium in the left ventricle. T2-weighted imaging **(C)** reveals a high-intensity area at the apex (white arrow) consistent with disturbed microcirculation due to fibrosis, thrombus formation, and hypokinesis of this area.

9 and 10; 11 and 12), and two sets of cousins (Table 1). Two large families (cases 1 and 2, and cases 5–8) were represented with high incidence of the disease, and the pattern we observed strongly implies an autosomal dominant inheritance of this disease. However, the other three sets of siblings were all male patients, supporting X-linked recessive genetic inheritance. One patient had a brother with RCM without INVM; another patient's father had hypertrophic cardiomyopathy.

Associated findings. Nine patients showed a dysmorphic facial appearance characterized by a prominent forehead, strabismus, low-set ears and a high-arched palate and micrognathia; six of these nine exhibited motor delay (Table 1).

Outcome. During follow-up, 16 patients showed gradually depressed systolic function based on echocardiography, and six showed decreased diastolic function based on Doppler echocardiography. Most of these patients have shown no symptoms related to the cardiovascular system and have required no medication. Eight patients have been treated with digoxin, diuretics, angiotensin-converting enzyme (ACE) inhibitors or vasodilators. Five patients with PSVT, frequent premature ventricular contraction (PVC), second-degree atrioventricular (A-V) block, or atrial fibrillation have required medication, and one patient with complete A-V block received an implantable transvenous pacemaker. Anticoagulant therapy was initiated in two patients to prevent thrombosis because intramural thrombi of the left ventricle were suspected on echocardiography.

Two patients died during the follow-up period. One (case 22) with left ventricular INVM died due to progressive ventricular dysfunction, complete A-V block and pulmonary embolism 13 years after the initial presentation of a heart murmur. The other patient (case 26) with biventricular INVM died from progressive and severe ventricular dysfunction and pulmonary embolism one year after presentation. One patient (case 15) is a candidate for heart transplantation as a result of severely deteriorated left ventricular function. These three patients all showed reduced left ventricular end-diastolic volume, high end-diastolic pressure and high mean pulmonary arterial pressure on cardiac catheterization, consistent with restrictive hemodynamic physiology (Table 3).

Although syncope and seizures were noted in two patients, systemic emboli were not clinically overt in any of the patients.

DISCUSSION

Despite the fact that the gross anatomic appearance and extension of the noncompacted myocardium observed on two-dimensional echocardiography are similar to features previously reported, the current study of Japanese children revealed several features dissimilar to those previously identified in the spectrum of INVM. Dissimilarities included a longer clinical course, no systemic embolic events, restrictive hemodynamic characteristics, a high incidence of WPW syndrome, rare ventricular tachycardia and a high incidence of family clusters that included female cases.

Long-term clinical course. In contrast with the symptomatic children previously reported by Chin and colleagues (11), most patients in this study were asymptomatic at initial presentation and have had a longer clinical course with gradual depression of left ventricular function. The previously reported patients manifested heart failure, arrhythmia or embolic events at initial presentation and experienced a rapidly progressive clinical course. These differences are probably due to the backgrounds of the study patients; our patients in part were detected incidentally through school screening examinations and our study was more population-based. In contrast to their investigation, there were no systemic embolic events or ventricular tachycardia in the current study, which may account for the favorable clinical course of our patients.

Similar to our investigation, Ritter and colleagues (17) reported a series of adults with INVM, including many asymptomatic patients who were identified through routine echocardiographic evaluations. Prognosis in the asymptomatic patients in their study was clearly better than the prognosis in the symptomatic patients, with a mean follow-up duration of 30 months. In contrast to their assumption, however, most patients in our study with a follow-up period longer than 10 years, whether symptomatic or asymptomatic, developed ventricular dysfunction. The fact that five out of eight patients in the asymptomatic group of the former study by Ritter and colleagues showed

cardiomegaly in the chest X-ray and therefore exhibited some form of ventricular dysfunction may not be at variance with our observation. Thus, ultimate outcome remains unclear, and further study will be needed to elucidate the long-term prognosis of asymptomatic patients with INVM.

Although the etiology of INVM is not fully elucidated, the disease is thought to be a morphogenetic abnormality that involves an arrest of compaction of the loose myocardial meshwork during fetal development. Therefore, INVM should be present at birth in all patients, whether ventricular dysfunction might become clinically overt during infancy, childhood or adolescence. In this respect, school screenings in Japan are appropriate for early identification of asymptomatic patients, and they are also valuable for clarifying the long-term natural course of this disorder. Although screening for INVM is only possible for an examiner familiar with the specific diagnostic pattern of the disease, echocardiography is a promising first-line diagnostic tool.

Electrocardiographic changes and arrhythmias. The incidence of WPW syndrome was higher in our series than that reported in adults; in contrast, LBBB was found much more frequently in this adult population (17). This difference between child and adult cases suggests that the ventricular conduction abnormality may develop later in life and could be due to progressive endocardial fibrosis in INVM. In children, LBBB is rare, and INVM should be considered in the differential diagnosis of the patient showing LBBB in childhood. The prolonged QRS duration of 180 ms or greater is a potential variable for monomorphic ventricular tachycardia. None of the patients showed a QRS duration of 180 ms or greater, which may account for the relative rarity of ventricular tachycardia in our series. The signal averaged ECG might detect areas of slowed conduction in the patients with INVM.

Only one case of WPW syndrome presenting with PSVT has been reported in the literature (11). The origin of the high incidence of WPW syndrome in our series of INVM remains unclear. The WPW syndrome is thought to arise from a failed regression of developmental embryologic atrioventricular anatomical and electrical continuity attributable to abnormal embryologic persistence of atrioventricular muscular continuity (29), which can also be seen in the failing regression of noncompacted myocardium in INVM. The study limitation is that WPW syndrome was diagnosed based on the surface ECG in this study. Definitive diagnosis of pre-excitation may require electrophysiologic testing.

Hemodynamic properties. Although the echocardiographic characteristics of numerous trabeculations and deep intertrabecular recesses have been well described and confirmed by necropsy, comparative hemodynamic properties assessed by cardiac catheterization have not been reported in children and adults. In this study, cardiac catheterization data in most patients showed normal left ventricular volume and increased left ventricular end-diastolic pressure, consistent with restrictive hemodynamics. In contrast, previous reports noted that patients with INVM usually presented with decreased left ventricular systolic function similar to that of DCM (11,17). Hook et al. (15) reported an exceptional case of INVM presenting as RCM, showing similarities to our data. This discrepancy in the hemodynamic characteristics may represent the different stages of the disease process. Patients who are symptomatic at presentation and who follow a rapidly progressive clinical course may show hemodynamic properties similar to DCM, whereas asymptomatic patients may follow a slowly progressive course of restrictive hemodynamic physiology, as our study has demonstrated. The complex anatomy of the abundant trabecular network may limit distensibility of the left ventricle and cause restrictive hemodynamics.

Furthermore, progressive subendocardial ischemia and subendocardial fibrosis, presumably related to isometric contraction of the penetrating intratrabecular recesses, might also contribute to the development of restrictive hemodynamics later in childhood.

Genetic background. Familial recurrence was encountered more often in pediatric population than has been reported in adults. A large family with six patients with INVM was reported by Bleyl et al. (18), and two sets of siblings were also reported previously (11). All reported cases were male, strongly suggesting X-linked recessive inheritance of this disorder. Supporting this notion, recent genetic analysis has presented evidence that mutations in the G4.5 gene on the Xq28 chromosomal region are responsible for the pathogenesis of INVM (19). The important finding of this study is that one-half of the familial cases in our series were female, suggesting heterogeneity in the inheritance pattern of this disorder.

Conclusions. Screening examination has been useful to find INVM in asymptomatic stages among Japanese children. Such children appear to have a longer clinical course with gradually depressed left ventricular function than do symptomatic children and adults. Although systemic embolic events and ventricular tachycardia, which account for high associated morbidity and mortality rates, were unusual in our series, the ultimate outcome of this rare disease remains unclear. Further study will be needed to elucidate its long-term prognosis. Because of the high incidence of family recurrence, echocardiographic evaluation of family members is warranted when INVM is found.

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